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## PENICILLIN THERAPY OF EARLY SYPHILIS\* FOLLOW-UP EXAMINATION OF 792 PATIENTS SIX OR MORE MONTHS AFTER TREATMENT

By DONALD M. PILLSBURY, M.D.

*Colonel, Medical Corps, Army of the United States; on leave from the Medical School, University of Philadelphia*

Penicillin was adopted as the drug of choice in the treatment of syphilis in the European Theatre of Operations, United States Army, on 26th June 1944. As from 15th June 1945, over 14,000 patients with early or latent syphilis, or with syphilis which had not responded satisfactorily to previous treatment with standard or intensive arseno-bismuth therapy, had received treatment with penicillin. This experience has afforded information regarding the toxicity of such therapy, its effect on the presenting lesions of syphilis, the incidence of infectious relapse, the incidence of persistently positive serologic tests for syphilis (hereinafter referred to as STS) from 6 to 9 months after treatment, and the results of examination of the cerebrospinal fluid 6 or more months after treatment. We have dealt almost entirely with early syphilis, and no attempt will be made in this report to summarize the available reports of the effect of penicillin upon late manifestations of syphilis.

The use of a short-term method of treatment for syphilis is a matter of urgent necessity under conditions obtaining in troops in an active theatre of military operations. Prolonged arseno-bismuth therapy, although successful in the individual patient, is not sufficiently simple or non-toxic to provide the maximum benefits of treatment to an adequate proportion of the patients in whom treatment is started. Significant and potentially disastrous lapses in treatment are all too common among civilians, and the difficulties of maintaining continuous long-term therapy become magnified many-fold in troops in the combat area. This was remedied to some extent in the United States Army in the European Theatre by the introduction of intensive arsenotherapy, and an account of our experience with this type of treatment was given before this Society in 1944 (Pillsbury and others). However, such therapy has the disadvantage of considerable inherent toxicity, involves a hospital stay averaging 25 days or more (with a 20-day schedule of treatment) and requires expert medical supervision.

### Introduction of penicillin treatment of syphilis

Following approval by the Surgeon-General of the United States Army, acting on recommendations from the Sub-Committee on Venereal Diseases of the National Research Council, penicillin therapy for syphilis was introduced in the European Theatre shortly after the invasion of Normandy. The criticism may be made that a method of treatment was adopted which had not been used over a sufficient period of time to enable us to judge its final curative effects. This is obviously true. The answer may be made, however, that the use of a short-term method of treatment for syphilis was imperative if even reasonably adequate therapy was to be available; there was no alternative. The initial results with penicillin therapy had indicated that it was probably the equal of intensive arsenotherapy in curative effect and was much superior on the score of toxicity, and on these grounds the decision was made.

It is not proposed, in this short report, to review the literature of the penicillin therapy of syphilis completely. The principal established facts of the American

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## THE BRITISH JOURNAL OF VENEREAL DISEASES

experience are summarized in the Appendix to this paper. The medical literature on this subject is only one of the lengthy bibliographies of reports of the treatment of various diseases with penicillin which have accrued since Sir Alexander Fleming's discovery of this remarkable compound. Credit for the original demonstration of the antisyphilitic properties of penicillin is due to Mahoney and his co-workers. Since the publication of their paper, the penicillin therapy of

TABLE 1—INITIAL DIAGNOSIS OF PATIENTS SUSTAINING  
CLINICAL RELAPSE (OR REINFECTION)

Stage of syphilis	Number of cases	Percentage of cases
Seronegative primary ... ..	7	85.9
Seropositive primary ... ..	9	
Primary (no data on STS reported) ...	45	
Secondary ... ..	3	4.2
Early syphilis, no other data ... ..	7	9.8
Total ... ..	71	

syphilis has been the subject of a major study by various civilian and Army agencies in the United States working under direction of the Sub-Committee on Venereal Diseases of the National Research Council. A monographic chapter on penicillin therapy will be found in the recent edition of Stokes's *Modern Clinical Syphilology*, and reviews of the present status of penicillin therapy were given at the International Conference on Venereal Diseases in St. Louis in November 1944, by Moore, Stokes, Mahoney, and others.

Many variations in the treatment of syphilis with penicillin have been introduced, including studies of penicillin combined with arsenoxide or bismuth or fever therapy, studies of penicillin administered in vehicles which prolong the absorption time of the drug, and studies of the comparative antisyphilitic effects of various fractions of penicillin. Treatment of syphilis with penicillin administered by mouth is just over the therapeutic horizon, however much weight of argument may be brought to bear against such a method of treatment, and it is very considerable. Concerning these methods, little has yet been published. It must be apparent to all observers that the possible variations in the methods of treatment of syphilis with penicillin, either alone or in combination with other measures, are enormous. Fortunately the initial clinical investigations were well conceived and have yielded basic preliminary information of great value. Much credit is due to the Sub-Committee on Venereal Diseases, under the chairmanship of

TABLE 2—TIME FROM ORIGINAL TREATMENT TO DIAGNOSIS  
OF RELAPSE (OR REINFECTION)

Period of time	Number of cases
Less than 4 weeks ... ..	6
4-8 weeks ... ..	13
8-12 weeks ... ..	14
12-16 weeks ... ..	16
16-20 weeks ... ..	10
20-24 weeks ... ..	3
24-28 weeks ... ..	3
32 weeks ... ..	1
45 weeks ... ..	2*
No data ... ..	5

\* One of these patients had sustained two relapses after penicillin therapy.

Dr. J. E. Moore, for its well balanced programme of investigation. As the supply of penicillin becomes sufficient for all civilian and military needs, many independent

## PENICILLIN THERAPY OF EARLY SYPHILIS

and isolated investigations will be undertaken. This is as it should be, if we are to preserve the democracy of science. It is to be hoped, however, that the situation will not become beclouded as it was for so many years after the introduction of arsphenamine. The medical literature of the past 25 years is replete with examples of both good and bad studies in syphilotherapy, some of which led to confusion and, at times, exerted an influence which denied to many thousands of patients the full benefits of correct principles of treatment ; but if those who run will but read, many of the mistakes of the past should be avoidable.

### Criteria of results

The principal criteria for evaluating any system of treatment for syphilis include (1) the initial effect on the presenting lesions of syphilis, (2) the control of infectiousness, (3) toxicity, (4) the incidence of clinical relapse, (5) the incidence of serological relapse, (6) maintenance or achievement of seronegativity, (7) the incidence of asymptomatic or symptomatic neurosyphilis, (8) the incidence of other late manifestations of syphilis, (9) the incidence of reinfection after treatment, and (10) the prevention of congenital syphilis. An attempt is made to analyse our experience with penicillin therapy on the basis of these criteria, insofar as our data permitted.

The system of treatment employed for all these patients consisted of injection of a total of 2,400,000 Oxford units of sodium penicillin, divided into 60 intramuscular injections of 40,000 units each at three-hour intervals, night and day,

TABLE 3—TYPE OF LESION NOTED AT TIME OF RELAPSE  
(OR REINFECTION)

Type of lesion	Number of cases
Penile, same site as original lesion ... ..	30
Penile, chancre at different site ... ..	10
Multiple penile lesions ... ..	6
Mucocutaneous, diffuse secondary type ...	18
No data ... ..	7
Total ... ..	71

for a total period of 7½ days. The directive letter outlining the penicillin therapy of syphilis in the United States Army in the European Theatre of Operations is reproduced in the Appendix. This directive is largely based on a War Department Technical Bulletin which was prepared with advice from the National Research Council. The use of combined penicillin and mapharsen in the re-treatment of patients who have failed to respond satisfactorily to previous treatment is a procedure which has been employed in the United States Army only in the European Theatre of Operations.

Since penicillin therapy is an experimental method of treatment, it was considered essential to employ a follow-up system which would do everything possible to protect the individual soldier against undetected relapse of his infection, and to obtain information which would be of value in arriving at a decision as to the efficacy of such treatment. Such a system had been developed previously in connexion with intensive arsenotherapy. (Acknowledgment is made of opportunity to observe the excellent Central Registry for Syphilis Cases in use in the Royal Canadian Army Medical Corps (Overseas) from which valuable suggestions were obtained.) All patients treated for syphilis with penicillin were reported by name, serial number and unit assignment to the Division of Medical Records, Office of the Chief Surgeon. At 2 and 4 months, respectively, a request for a quantitative Kahn test on such patients was sent to the unit of the patient, and at 6 months a request was made for a complete spinal fluid examination, quantitative Kahn test and physical examination. Further requests for quantitative Kahn tests were made at 9 and at 12 months.

**Initial effect on the presenting lesions of syphilis**

Penicillin has, in our experience, a more regular and more rapid effect on lesions of early syphilis than has any arsphenamine compound. The evidence on this point is agreed to by all observers. Lesions of early syphilis, unless markedly ulcerated or indurated, are ordinarily healed on completion of the course of treatment. A single exception has been noted in a report from the 198th United States General Hospital, as follows.

*L. C. B., Negro.* Received treatment for syphilis, primary, manifested by a dark-field positive penile lesion and a positive STS, with penicillin administered between 12th and 19th April, a total of 2,400,000 units. On 9th May the patient was readmitted to hospital because of persistence of the penile ulcer and development of a secondary eruption. The Kahn serologic test was positive, 80 units. The spinal fluid examination was negative. The patient was re-treated with a total of 4,000,000 units of penicillin and 480 milligrams of mapharside (8 daily injections of 6 milligrams each). *Chen*

The circumstances in this case suggest that the original supply of penicillin may have been impotent, but there is no other evidence on this point.

In some patients in whom a mucocutaneous relapse has been reported, it has been noted that the induration at the site of the chancre had not disappeared entirely after the first course of penicillin, although epithelization was satisfactory. In such patients relapse ordinarily occurs within a few weeks of completion of treatment (Clark ; Tomskey).

**Reactions to treatment**

In our entire series of patients, only one report has been received of a reaction to penicillin sufficient to cause interruption of treatment (Showstack). Compared with any type of arsphenamine or heavy metal therapy, this is an extraordinarily favourable experience. In Showstack's patient, an urticarial reaction of sufficient degree to preclude further penicillin therapy developed midway in the course of treatment. Occasional instances of mild to severe urticaria or angioneurotic oedema have been noted up to 10 days following completion of treatment, but these reactions have been essentially minor in character. To date in our experience, therefore, treatment of syphilis with penicillin has proved to have an almost negligible incidence of toxicity.

Hershheimer reactions, of either local or febrile type, have occurred in 25-50 per cent of patients, although the exact incidence is not determinable from the

TABLE 4—SEROLOGIC TEST FOR SYPHILIS AT TIME OF RELAPSE (OR REINFECTION)

Result	Number of cases
Positive STS ... ..	41
Negative STS ... ..	8
Doubtful STS ... ..	2
No data ... ..	20
Total ... ..	71

available data. This reaction is well recognized (see par. 5 of Appendix) and constitutes no contraindication to further treatment in early syphilis. Our experience in the treatment of late syphilis in adults is not sufficient for us to offer any opinion based on personal observation but, in focal syphilitic involvement of a vital structure, it would seem to be advisable to proceed with a much reduced initial dose. Stokes has emphasized the necessity of caution in the treatment of early congenital syphilis, especially in weak debilitated infants.

**Incidence of relapse**

A survey was recently conducted among United States Army medical installations on the European Continent of the incidence of clinical relapse

## PENICILLIN THERAPY OF EARLY SYPHILIS

observed after penicillin therapy for syphilis administered prior to 1st May 1945. Of 75 medical installations reporting, 27 had treated one or more patients who had had infectious relapse or reinfection following penicillin therapy. The available information in regard to the original diagnosis in these patients, the time at which relapse occurred, and the type of relapse noted, is given in Tables 1, 2 and 3.

The number of patients with early syphilis to whom these instances of relapse are applicable can be estimated only within wide limits, since the total number is

TABLE 5—RESULTS OF BLOOD KAHN TEST SIX OR MORE MONTHS AFTER PENICILLIN THERAPY

Original diagnosis	Total no. of cases	STS negative at		STS negative Total	Percentage
		9 months	6 months		
Seronegative primary ... ..	274	34	235	269	98·18
Seropositive primary ... ..	271	33	205	238	87·82
Secondary ... ..	111	14	66	80	72·07
Other types (latent, etc.) ... ..	40	4	18	22	55·00
Types unknown (diagnosis not reported) ... ..	96	12	68	80	83·33
Totals ... ..	792	97	592	689	86·99

dependent upon factors of attrition and movement of personnel which are not exactly determinable. It is reasonably certain, however, that these figures apply to not less than 5,000 nor more than 8,000 cases of penicillin-treated early syphilis. This would yield an incidence of infectious relapse or reinfection of the order of 1·2 per cent in patients observed 1–10 months after treatment. This is regarded as a favourable experience. Good evidence for reinfection was present in only one patient of the entire series of 71 instances of “relapse” (Holman). It is oftentimes difficult or impossible to distinguish between relapse and reinfection, even with all essential data concerning the patient at hand. In 10 other patients, occurrence of a primary lesion at a site other than the original one, following an observed period of seronegativity and a history of infectious contact, indicated that the patient might have sustained a reinfection rather than a relapse. It is believed that reinfection will be encountered frequently following penicillin therapy of syphilis, but from the data available in our patients the incidence of relapse versus reinfection cannot be determined.

The data in our cases have not yet been analysed sufficiently to indicate the incidence of serologic relapse except in seronegative primary syphilis, in which the serologic relapse rate has been 1·82 per cent for patients observed for a period of 180–240 days after treatment.

### Seronegativity 180–240 days after treatment

In the American Army it is standard practice to perform a preliminary “test of cure” when 6 months have elapsed since treatment was administered. This examination includes a quantitative Kahn test of the blood, complete spinal fluid examination and a physical examination for evidence of mucocutaneous or visceral relapse. Experience has demonstrated that these examinations are, in actual practice, performed at some time between 6 and 8 months after treatment in most cases. In response to routine follow-up letters, data had been obtained in 792 cases at the time this report was written. The results of the STS in these patients are given in Table 5.

It will be noted that a considerable variation exists in the percentage of cases achieving seronegativity, depending upon the stage of syphilis at the time of treatment. Of 274 patients with an original diagnosis of seronegative primary syphilis, 98·18 per cent were seronegative 6 or more months after treatment; 87·82 per cent of seropositive primary syphilis cases had achieved seronegativity; 72·07 per cent of the patients with secondary syphilis were seronegative at that date. This may be compared with the experience after 20-day intensive arseno-bismuth therapy (see Table 6).

## THE BRITISH JOURNAL OF VENEREAL DISEASES

This difference in maintenance or achievement of seronegativity is the sole criterion on which, in our experience, penicillin compares unfavourably with arseno-bismuth therapy. Of the total of 103 patients who had a positive STS 6 or more months after penicillin therapy, 44 showed a very low titre of the quantitative Kahn test (below 10 units). It is probable that a considerable percentage of these patients would eventually achieve a satisfactory result without further treatment. Nevertheless, on the basis of all previous experience after conventional or intensive arseno-bismuth therapy, it is believed that such patients must be considered to be in greater danger of relapse or progression of their infection than

TABLE 6—RESULTS OF BLOOD KAHN TEST SIX OR MORE MONTHS AFTER  
20-DAY INTENSIVE ARSENO-BISMUTH THERAPY

Stage of syphilis	Number of cases followed	Number negative	Percentage negative
Primary seronegative ...	454	448	98.68
Primary seropositive ...	367	349	95.10
Secondary ... ..	123	114	92.68
Latent (principally early) ...	38	29	76.32
Totals ...	982	940	95.7

are patients with a negative STS. Further studies may indicate that such a prediction is not justifiable after penicillin therapy, unless a high or increasing titre is noted. It is understood that the National Research Council observes the policy of not re-treating such patients for one year unless the quantitative titre shows a significant sustained rise; the results of observation of patients with a low titre will be followed with interest.

### Incidence of asymptomatic neurosyphilis

Reports have been received of the results of examination of the spinal fluid of 642 patients, 6 or more months after completion of treatment. In 3 of these, minor changes, including slight rise in the cell count and in the total protein content, have been noted. In none of the fluids was the complement-fixation test positive. This is a very encouraging record within the time limits of observation. Frank neuro-recurrence will undoubtedly be encountered in an occasional patient after penicillin therapy, but its absence to date in 642 patients in this series would lead one to predict that it will be uncommon.

### Summary and discussion

*Penicillin and arsenotherapy.*—An attempt has been made in Table 7 to compare the results of penicillin treatment of syphilis with standard and intensive arsenotherapy, on the basis of various criteria. It is considered that penicillin has an overwhelmingly proved superiority over any other method of treatment on the scores of non-toxicity of treatment, completion of treatment within the prescribed time, rapid and regular disappearance of presenting lesions of syphilis, and control of infectiousness. Our results to date indicate that it will prove to be preventive of neurosyphilis in a very satisfactory percentage of patients with early syphilis. The one score on which penicillin has proved to be inferior to intensive arseno-bismuth therapy, to date, in our experience, is in regard to reversal of the STS to negative in seropositive early syphilis 6 or more months after treatment. Such patients have been re-treated, in our series, because the evidence is still lacking that such a finding is of no serious significance.

*Early diagnosis.*—It is readily apparent that early diagnosis is essential if the curative effects of a single course of penicillin in syphilis are to be fully exploited. Among military personnel it is possible to raise the percentage of syphilis diagnosed in the seronegative primary stage to at least 50 per cent of all cases of early syphilis, by continual emphasis to medical officers of the necessity of referring promptly

## PENICILLIN THERAPY OF EARLY SYPHILIS

to a centre for diagnosis all patients with penile ulcers of any type. Among patients in civil life it cannot be expected that as high a proportion of cases will be diagnosed before the STS has become positive, both because of the lower index of suspicion and because of the much higher proportion of female patients.

*Coincident gonorrhoea and syphilis.*—The activity of penicillin against a wide variety of micro-organisms has introduced a new problem in the field of syphilotherapy. Never before has there been a drug which, when given internally, exerted a curative or suppressive effect upon both syphilis and gonorrhoea. It is apparent that the dose of penicillin used in the treatment of gonorrhoea, that is, of the order of 200,000 units, will rarely have a satisfactory curative effect upon a syphilitic infection previously acquired. Nevertheless, such a dose is entirely sufficient to suppress the development of signs of early syphilis, or to produce healing of mucocutaneous lesions which are already present. In the treatment of gonorrhoea with penicillin, therefore, it is essential that patients be subjected to a complete physical examination for evidence of early syphilis before penicillin treatment is administered. If any such lesions are present, it is obviously desirable that a sulphonamide be administered for the gonorrhoeal infection until the status of the patient in regard to syphilis is determined. It is equally advisable that every patient with gonorrhoea should have a serologic test for syphilis prior to administration of treatment. It is obviously not feasible or necessary, however, to await the results of this test before treatment of the gonorrhoeal infection.

TABLE 7—COMPARISON OF STANDARD, INTENSIVE AND PENICILLIN THERAPY

STANDARDS OF COMPARISON	PROLONGED ARSENICAL AND HEAVY-METAL THERAPY	20-DAY INTENSIVE ARSENO-BISMUTH THERAPY	PENICILLIN THERAPY
Toxicity of treatment ...	Mortality almost nil with mapharsen-bismuth system. Incidence of minor reactions high	Potential mortality from treatment 0.1-0.2%, chiefly in female patients. Moderate to severe reactions common: 10-20%	Mortality and morbidity nil for all practical purposes
Completion of scheduled treatment.	Highly variable: 20-80%. Dependent upon many factors, many of which are not always controllable	95% of all patients	Practically 100%
Infectious relapse ...	1-15%, depending upon regularity of treatment; up to 2 years	3-5%; usually within 6 months	Low (on basis of 1-10 months' observation; many cases probably reinfection)
Incidence of asymptomatic neurosyphilis in patients completing treatment ...	10%	1%	1% or less (predicted)
Reversal of positive serologic test for syphilis	12-16 weeks	12-16 weeks	12-16 weeks; high initial titre requires longer time for reversal
Absence from military duty ...	Variable; theoretically low, but absence of half day for each treatment is common	25-30 days	10 days (including time for diagnosis); immediate return to full activity almost always possible
Treatment facilities required ...	Out-patient clinics	Hospital; special facilities for study and treatment of reacting patients essential	Hospital or barracks
Negative STS 180-240 days after treatment ...	Variable, dependent upon regularity of treatment	98% in seronegative primary; 95% in seropositive primary; 92% in secondary	98% in seronegative primary; 87% in seropositive primary; 72% in secondary

The question of follow-up tests for syphilis after penicillin treatment of gonorrhoea has not been completely settled. It is not known for how long such treatment may suppress physical or serological evidence of syphilis which was in the stage of incubation at the time the treatment for gonorrhoea was given. It may well be questioned whether a serological test taken 3 months after such

treatment is adequate ; it is probable that a test at both 3 and 6 months would be advisable.

*Other medical or surgical infection.*—In addition to patients with gonorrhoea are those to whom penicillin is administered for some other medical or surgical infection. There is great danger that the status of such patients in regard to syphilis may be greatly beclouded for future evaluation. An example may be cited of a patient treated with penicillin for an acute febrile illness. A serological test for syphilis taken prior to the administration of penicillin is reported positive several days later, after some penicillin has been administered. Was this a non-specific positive reaction due to a febrile disease ? Does the patient have syphilis ? Should full treatment for syphilis be given ? The answers to these questions are not clear cut at the present time. It is believed, however, that treatment with a full course of penicillin as for early syphilis should be administered, and that every effort should be made to determine whether or not the positive serological test was specific.

*The Herxheimer reaction.*—It is the belief of many observers that the febrile Herxheimer reaction observed after initiation of penicillin treatment of early syphilis is a highly specific one for this disease. I have never observed it in connexion with penicillin treatment of any disease which had previously been non-febrile. If, therefore, such a febrile reaction occurs after the first or second injection of penicillin in the treatment of gonorrhoea, examination of the patient for collateral evidence of syphilis should be repeated and thorough. There is much to recommend continuance of penicillin therapy in such cases up to a total dose of the order of that recommended for early syphilis.

*Indications for penicillin treatment.*—With increasing experience of penicillin in syphilis, the question of how best to employ this extraordinarily valuable agent in early syphilis should soon come to the fore. Based on our own experience, the results in seronegative primary syphilis are highly satisfactory. In frank secondary syphilis, on the other hand, the incidence of persistent seropositivity after 6 months of observation is considerably higher. It is also probable that the greatest incidence of mucocutaneous relapse will be found eventually to occur in this group. On this basis, therefore, it is possible that patients with secondary syphilis will require additional treatment in order to produce a satisfactory overall incidence of cure. Should it be an increased amount of penicillin given over a longer time ? Should it be penicillin combined with another antisyphilitic agent ? Although re-treatment of relapse with penicillin is apparently satisfactory in regard to immediate effects, is it justifiable to let a considerable proportion of patients with secondary syphilis undergo the risk of relapse ? Relapsing syphilis is bad syphilis, and one hesitates to place all one's therapeutic eggs in the penicillin basket for such patients. At the present time, it is my personal belief that frank secondary syphilis should be treated with a combination of penicillin and mapharside. The schedule outlined in the Appendix should be satisfactory for male patients, provided that the medical supervision is adequate. For female patients, however, wider spacing of the injections of the arsenical (not oftener than 3 times weekly) is advisable, because of the much increased incidence of serious reactions to intensive arsenotherapy in the female.

## Conclusions

- (1) The toxicity of penicillin therapy in early syphilis is negligible.
- (2) Infectiousness is controlled promptly, with rare exceptions.
- (3) The incidence of infectious relapse after penicillin therapy is low. It is suggested by our results that infectious relapse will usually occur within 20 weeks after treatment. The lesions of relapsing syphilis will appear most frequently on the genitalia.
- (4) Realization of the full benefits of a single course of penicillin therapy in syphilis is dependent upon the promptness with which the diagnosis of syphilis



## PENICILLIN THERAPY OF EARLY SYPHILIS

is made after infection. Achievement of seronegativity 6 months after the initial treatment is significantly lower in seropositive primary and in secondary syphilis than in seronegative primary syphilis.

(5) The incidence of asymptomatic neurosyphilis, disclosed by spinal fluid examination performed 6—8 months after treatment, is extremely low, especially as compared with the incidence after standard arsphenamine and heavy metal therapy.

(6) The initial promise of penicillin as the best single agent against syphilis is being fulfilled. The necessity of admitting patients to hospital for treatment is an important drawback to the general application of penicillin therapy for syphilis in a civilian population. The evolution of methods of administration which would permit treatment in a doctor's office or out-patient clinic would be of great value.

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## APPENDIX

### HEADQUARTERS

#### EUROPEAN THEATER OF OPERATIONS

#### UNITED STATES ARMY

#### Office of the Chief Surgeon

27 February 1945

### CIRCULAR LETTER NO. 20

#### The Treatment of Syphilis

1. *The purpose of this Circular Letter* is to outline certain changes in the management of syphilis, based on increasing experience with penicillin therapy. It is, in part, abstracted from WD Technical Bulletin 106, 11 October 1944, with additions based on the experience in ETO.

#### 2. *Indications for Penicillin Treatment of Syphilis.*

Penicillin will be used in the treatment of the following types of syphilis:

- Untreated primary and secondary syphilis.
- Untreated latent syphilis. It is essential that a preliminary spinal fluid examination be made in all cases of presumed latent syphilis. If the spinal fluid is abnormal, the case must be classified as asymptomatic neurosyphilis and be managed according to par 8a below.
- Neurosyphilis.

#### 3. *Indications for combined Penicillin-Mapharsen Therapy for Syphilis.*

a. Treated primary and secondary syphilis that has failed to respond to Mapharsen-bismuth therapy, or to intensive arsenotherapy, or to penicillin therapy, as the case may be. This includes:

- Clinical relapse, such as mucocutaneous, ocular, osseous, or visceral.
- Treatment resistance, a rare condition, manifested by failure of the primary and secondary lesions to respond to adequate mapharsen-bismuth therapy, usually accompanied by the presence of living treponemas in the lesions.

(3) Serologic relapse as evidenced by reversal of a negative STS (serologic test for syphilis) at the conclusion of Mapharsen-bismuth therapy to positive during the 6 months post-treatment observation period, or during the 12 month observation period following intensive arsenotherapy or penicillin therapy. The criteria of serologic relapse are discussed in paragraphs 8b and c below.

(4) Serum-fastness as evidenced by a persistent positive STS at the end of mapharsen-bismuth therapy, or six months after intensive arsenotherapy or penicillin therapy.

#### 4. *Technique of Penicillin Treatment of Syphilis.*

- Penicillin therapy requires hospitalization of approximately 10 days, including 7½ days

## THE BRITISH JOURNAL OF VENEREAL DISEASES

of therapy, and time consumed for pretherapeutic diagnostic procedures and administrative details.

b. Dosage and technique of administration of penicillin. The total dosage will be 2,400,000 units of penicillin, given in 60 consecutive intramuscular injections of 40,000 units (2 c.c. of solution) each, at 3-hour intervals day and night for 7½ days. No additional anti-syphilitic therapy is to be given after the completion of the course except in the case of asymptomatic neurosyphilis.

c. Noninterruption of penicillin treatment. Treatment should continue without interruption after its initiation. On the first day of treatment, commonly, and during the course of treatment less frequently, minor reactions may be encountered. These are almost never an indication for the discontinuance or interruption of therapy.

### 5. Reactions observed in Penicillin Treatment of Syphilis.

a. Herxheimer reactions. These occur frequently in cases of primary and secondary syphilis, less commonly in cases of latent syphilis, and rarely in cases that have already received some anti-syphilitic therapy. The manifestations may be focal or systemic and are ascribed to the massive destruction of treponemas in the syphilitic lesions and in the blood stream. These reactions may therefore be considered of favourable significance. Both the focal and systemic Herxheimer reactions are encountered on the first day of treatment only. They begin usually some 3 to 6 hours after the first penicillin injection, gradually become worse and reach a peak, after which they slowly and progressively subside, disappearing within an average of 24 hrs. No specific therapy is required although such drugs as aspirin and codeine may be given for relief of symptoms. It must be emphasized that these symptoms disappear spontaneously in spite of the continued regular administration of penicillin, and are not justification for discontinuance of penicillin.

(1) The focal Herxheimer reaction consists of an aggravation of the existing syphilitic lesions. There may be increased swelling of the chancre, further increase of already enlarged regional lymph nodes accompanied by pain, and exaggeration of the secondary eruption. A pallid, sparse, macular eruption often becomes extremely profuse and vividly red, and may resemble measles or scarlet fever.

(2) The systemic Herxheimer reaction may be manifested by a variety of symptoms, such as headache, malaise, nausea, occasionally vomiting, abdominal cramps and weakness, but its most characteristic features are chilly sensations and fever. Peak temperatures above 105°F have been recorded, although generally lower grades of fever prevail.

b. Other reactions to penicillin. Other reactions caused by penicillin have been rare and ordinarily trivial. Most patients will complain of more or less muscle soreness at the site of injections, but usually this is not objectionable. The most common late systemic reactions have been secondary fever occurring toward the end of treatment and terminating immediately on its cessation; urticaria; generalized pruritus; erythema nodosum lesions; mild erythema multiforme; diffuse toxic erythema-like eruptions; herpes simplex; nausea, and occasionally vomiting.

### 6. Post-treatment Observation of Patients Treated for Syphilis with Penicillin.

#### a. Serologic and Clinical Follow-up.

(1) All syphilis cases treated with penicillin will have a physical inspection and quantitative STS at the following times after treatment:

Two Months.  
Four Months  
Six Months  
Nine months  
Twelve Months

(2) On each specimen of blood the laboratory should be requested by the medical officer to perform the authorized quantitative STS described in TM 8-227, and to report the result in units.

#### b. Spinal fluid

(1) In primary and secondary syphilis the spinal fluid will be examined as soon as feasible after the completion of 6 months of observation. In no case will the syphilis register be closed until this examination has been accomplished.

(2) Spinal fluid tests to be performed. Cell count; Pandy or Nonne-Apelt qualitative tests for protein; quantitative estimation of total protein; complement fixation (Wassermann) test, or, if this is not feasible, a flocculation protein determination should be performed at the local laboratory within 30 minutes after the spinal fluid is withdrawn.

#### c. Special administrative features of penicillin treatment.

(1) Because the long-term effects of penicillin in the treatment of syphilis have not yet been determined, it is vital that all concerned cooperate in ensuring that adequate follow-up studies are made. The Commanding Officer of each U.S. Army hospital in the ETO will submit a monthly listing of patients who have received penicillin therapy for syphilis during the month.

(2) Preparation of the Syphilis Register W.D., M.D. Form No. 78. This will be filled in completely in the usual manner, and a brief note describing the treatment procedure will be made in the Register. A sample note reads as follows:

## PENICILLIN THERAPY OF EARLY SYPHILIS

Soldier received intensive penicillin therapy from 1 Nov. 1944 to 8 Nov. consisting of 60 consecutive intramuscular injections of 40,000 units each at 3-hour intervals for a total dose of 2,400,000 units. There was a febrile Herxheimer reaction the first day with peak fever of 102.4°F. Lesions were healed when therapy was completed.

(3) Preparation of W.D., M.D. Form No. 78a (Patient's Record of Syphilis Treatment). This will be prepared as a personal record for the soldier. A brief account of the treatment status of the patient will be entered. This can be done simply by repeating the note made in the Syphilis Register, described in (1) above. An additional statement will be made regarding the follow-up measures to be carried out.

(4) Closure of Syphilis Register.

(a) Primary and secondary syphilis. On completion of the spinal fluid examination and physical examination six or more months after penicillin therapy has been given, providing the results are satisfactory, the Syphilis Register will be sent to the Office of the Chief Surgeon (Attention Medical Records Division) for review.

(b) Latent Syphilis. The Syphilis Register will be closed in latent syphilis and transmitted to the Office of the Chief Surgeon, Medical Records Division, after twelve months of observation if there has been no clinical or serologic relapse, even though the serologic tests have remained persistently positive. It is anticipated that serum-fastness will not be uncommon in cases that receive penicillin therapy in the latent stage of syphilis.

### 7. *Clinical and Serological Post-Treatment Course of Favorably Responding Penicillin-treated Syphilis.*

a. Primary and Secondary Syphilis.

(1) Clinical course. The rate of healing of primary and secondary syphilitic lesions varies, depending principally upon the type of lesion. Large ulcerated or deeply infiltrated lesions may not heal completely for 1 to 3 weeks after treatment is concluded. Presence of such lesions, unless physically incapacitating, or requiring extensive local treatment, will not be cause for prolonged hospitalization.

(2) Serologic course. The titre of the STS declines gradually from positive to negative in the post-treatment period, the negative phase being achieved in a variable time. The majority of cases become negative between the second and fourth post-treatment months, although earlier and later reversals occur. In general, the higher the initial titre of the quantitative STS the longer the test will take to become negative.

(3) Critical relapse period on the basis of present information. The critical period for relapse, both clinical and serologic, appears to lie between the third and sixth post-treatment months, although relapses have been observed at earlier and later periods.

b. Latent Syphilis.

(1) Serologic course. The serologic curve may take the same course as that observed in primary and secondary syphilis, notably those which have only recently passed from the secondary phase into the phase of latency. On the other hand, individuals with older latent syphilis are likely to exhibit serologic refractoriness, the STS showing little or no tendency to fall in titre.

### 8. *Definition of Penicillin Failure.*

Care should be exercised in the determination of failure since patients may develop intercurrent skin eruptions of nonsyphilitic character. Intercurrent infections and smallpox vaccination may produce a temporary elevation of the titre of the quantitative STS. All forms of clinical relapse are generally accompanied by serologic relapse, or by persistently high serologic titres. Treatment failures may be divided into nine categories.

a. Mucous and/or cutaneous relapse is manifested by the appearance of syphilitic lesions of the mouth, genitals, and skin, the latter especially in the anogenital region. Darkfield examinations should be performed to corroborate the diagnosis. If darkfield examination is negative, repeated quantitative STS should be performed which will reveal a progressively rising titre.

b. Serologic relapse is manifested by a rising titre of the quantitative STS after the test had become negative or has previously manifested a falling trend. When a serologic relapse is suspected, the patient should be thoroughly and completely examined, since serologic relapse is usually accompanied or shortly followed-up by mucocutaneous or some other clinical relapse. Since the titre of the quantitative STS may vary from time to time, as a result of laboratory technique, and in different laboratories, it is not sufficient to accept minor fluctuations in the titre as evidence of serologic relapse. Serologic relapse should be diagnosed only when a series of consecutive tests, performed preferably in the same laboratory, shows persistently increasing titres over a period of 3 to 4 weeks.

c. Serum-fastness in primary and secondary syphilis is manifested by a failure of the quantitative STS to show a marked decline within an arbitrary period of six months after completion of therapy. Minor fluctuations in the titre may be observed, but there is no consistent, gradual and maintained fall to negative. This condition will apparently be uncommon in primary and secondary syphilis, where it will be considered a treatment failure when present 6 months after completion of therapy. It will not be uncommon in latent syphilis, in which it will not be considered a treatment failure.

d. Neurologic relapse (neuropsychic) may occur as acute syphilitic meningitis, with headache, dizzy spells, fever, and rigidity of neck. In fulminant cases, coma may supervene rather rapidly. Less commonly relapse in the nervous system may appear as an isolated cranial

## THE BRITISH JOURNAL OF VENEREAL DISEASES

nerve palsy or paralysis of one or more extremities. Diagnosis should be confirmed by spinal fluid examination, and a neurologist should be consulted for diagnostic assistance.

e. Asymptomatic neurosyphilis is manifested only by an abnormal spinal fluid.

f. Ocular relapse may be manifested by iritis, usually unilateral, or optic neuritis, or neuroretinitis, which may be unilateral or bilateral. An ophthalmologist should be consulted.

g. Osseous relapse is manifested by severe pain, often nocturnal, in the long bones, most often the tibiae, or severe headaches when cranial bones are affected. Local tenderness is often very acute.

h. To date, no instance of true treatment resistance to penicillin insofar as failure of mucocutaneous lesions to heal or treponemas to disappear, has been observed.

### 9. Management of Penicillin Failures.

a. Cases of neurologic relapse and asymptomatic neurosyphilis will receive a total of 4,000,000 Oxford units of penicillin while in hospital, and then be managed in accordance with the directions contained in Circular Letter No. 103, "Management of Neurosyphilis", Office of the Chief Surgeon, 9 August 1944. The penicillin will be administered in 80 consecutive injections of 50,000 units each at 3-hour intervals day and night for 10 days. In patients in whom the possibility of a severe Herxheimer reaction may be considered to have serious potentialities, the initial doses of penicillin may be reduced to 10,000 units, but it should be possible to reach the full dosage schedule within 48 hours. Patients with Grade I and II spinal fluids will be continued on standard mapharsen-bismuth therapy after completion of the penicillin course.

b. Patients with other types of treatment failure will receive a second course of treatment consisting of concurrent administration of penicillin and Mapharsen, as follows:

Penicillin: 80 injections of 50,000 units each given intramuscularly at 3 hour-intervals day and night for ten days, a total of 4,000,000 units.

Mapharsen: 60 mgms. intravenously daily for 8 days, a total of 480 mgms.

(1) Management of reactions to Mapharsen. Certain patients will prove more or less intolerant to Mapharsen given in accordance with the above schedule. However, unless the patient has previously received Mapharsen, it is not likely that such reactions will develop prior to the 5th day of treatment. The reactions to be looked for are:

(a) Fever. Severe reactions to intensive arsenotherapy of this type almost never occur in the absence of accompanying or preceding fever. In any patient showing a rise in temperature above 100°F, the patient should be carefully examined clinically, especially for the reactions listed below, and adequate laboratory studies performed.

(b) Toxic encephalopathy.

(c) Neutropenia.

(d) Toxicodermal reactions of various types, usually a morbilliform or scarlatiniform eruption accompanied by fever.

(e) Hepatitis.

(2) A reaction to Mapharsen of more than slight severity is an indication for discontinuance of such medication. The penicillin course will be continued to completion, and the patient then placed on observation.

(3) Patients with severe reactions to Mapharsen should be treated with injections of BAL, four injections of 2 c.c. each during the first 24 hours, and 2 c.c. daily for the next four days.

### 10. Management of patients already on standard Mapharsen-bismuth treatment for syphilis who receive penicillin for a surgical wound or an intercurrent medical infection.

Insofar as is possible without prejudice to the general medical and surgical treatment of such patients, penicillin therapy to a total of 2,400,000 units should be given while the patient is in hospital. The patient will then be placed on observation as far as his syphilitic infection is concerned. It is impossible at present to evaluate the influence of partial courses of penicillin in the cure of syphilis, and it is important, therefore, that the full course of penicillin be given before the patient is placed on observation.

## THE TREATMENT OF GONORRHOEA WITH PENICILLIN\*

By J. MARSHALL, M.D.

Lieutenant-Colonel, R.A.M.C.; Command Venereologist, Eastern Command and London District

Although penicillin has been used in the treatment of gonorrhoea for a short time only, it has already established itself as the most valuable remedy for this disease that has yet been discovered. The short life history of the gonococcus and the relative accuracy of tests for cure have made the assessment of the value of penicillin more simple and accurate in gonorrhoea than in syphilis.

Penicillin became available to the medical services of the Armed Forces in 1944 at a most opportune time, and its use then in cases of sulphonamide-

\* An address to the Medical Society for the Study of Venereal Diseases, 28th July 1945.